#1230

Comm.
Dr. Bing
Dr. Gardner
Dr. Sommers

PHARMACOLOGY

THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application for Research Grant
(Use extra pages as needed)

NOV 26 1973

Date: 11/15/73

1. Principal Investigator (give title and degrees):
Walter B. Essman, M.D., Ph.D.
Professor of Psychology & Biochemistry

2. Institution & address:
Queens College of the City University of N.Y.
65-30 Kissena Blvd.
Flushing, New York 11367

and

The Research Foundation of the City University of N.Y.
1411 Broadway
New York, New York 10018

3. Department(s) where research will be done or collaboration provided:
Psychology, Biochemistry

4. Short title of study: "Studies of Nicotine Action Upon Memory Consolidation"

5. Proposed starting date: April 1, 1974

6. Estimated time to complete: 36 months (3 years)

7. Brief description of specific research aims:

The aims of the proposed research are to extend the current active work concerned with the relationship between nicotine action upon regional cellular and subcellular sites in the central nervous system to the process of memory consolidation. Such investigation will, more specifically, concern (1) the effects of nicotine action as a function of development; (2) the effect of nicotine and several of its metabolites in several inbred strains of mice, utilizing the proposed methods in this investigation; (3) the relationship of age as well as strain to centrally induced amnesia phenomena and their interaction with nicotine and (4) concern the relationship between nicotine effect and memory consolidation on a cellular level.

The aims thereby, of this proposed project are to relate two important parameters to the findings that have already emerged in the relationship between nicotine action,

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7. Brief description of specific research aims: continued from previous page.

metabolism, and mediation of central aminergic changes to memory consolidation. Because of the potential significant contribution that nicotine holds for extending the memory consoldiation process, and on more pragmatic grounds, for nicotine neuropharmacology, the important parameters of age and strain would appear to warrant more detailed consideration in this context.

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8. Brief statement of working hypothesis:

Within defined parameters of time and dosage, nicotine and several of its centrally active metabolites can alter the time course and nature of the memory consolidation process; also, the relationship between this observation and several cellular and regional alterations in amine metabolism might be modified; the facilitation of memory consolidation by nicotine treatment can be modified as a function of age from the specific strain in which treatment regimen is being observed. Endogenous differences in the regional and cellular characteristics of these biogenic amines with which both nicotine or amnesic agents or effects interact, is determined by age differences and/or strain differences that will contribute to a more fundamental understanding of the relationship between nicotine action and memory consolidation.

9. Details of experimental design and procedures (append extra pages as necessary)

The behavioral portion of all the experiments to be carried out will employ the single trial conditioning procedure, previously described in our protocols for establishing a stable avoidance response in one trial. This response, which is stable over time as well as within experimental conditions, has been successfully utilized to assess the amnesia effect of electroconvulsive shock, and other agents or events which, when presented in close temporal proximity with the acquisition trial experience, result in a reduction in the incidence of retention, as measured 24 hours later; amnesia and/or retention are assessed by measures of response latency so that criterion avoidance is defined on the basis of latencies in excess of five standard deviations of the mean latency exhibited on the training trial and an absence of retention, or retrograde amnesia, is defined as a response latency on the testing trial that is equivalent to or within one standard deviation of the mean response latency shown on the training trial. This procedure has been successfully utilized in our laboratory with over 20,000 mice during the nine to ten years within which the technique was originally devised by this investigation. A more detailed description of procedure, parameters governing acquisition and retention, and some of the applications thereof, may be found in several publications (Essman & Alpern, 1965; Essman, 1968; Essman and Essman, 1969).

Animals utilized in all of the proposed studies will be mice that will either be

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9. Details of experimental design and procedures -- continued from previous page.

obtained from a commercial vendor or specifically bred through vivarium facilities located within the investigator's laboratory, for precise control over age differences. The strains of mice to be utilized will include CF-1S strain (Carworth Farms, New City, New York), which have been employed throughout the course of previous investigation; C-57 BL/6J, a strain of mouse which in previous experiments has shown highly efficient learning ability, has demonstrated a profoundly decreased susceptibility to the amnesic effects of several post-training treatments producing retrograde amnesia. Previous experience with this strain has included only learning ability animals, and the use of this strain with nicotine has not been employed. It is also our experience that whole-brain 5-HT levels in this strain are somewhat higher (0.75 µg/g) than average values (0.49 µg/g) obtained at comparable ages for CF-1S strain mice. A somewhat more emotionally labile mouse will be selected for the 3rd strain included within this series, the DBA strain. This strain of animal has, in previous experience, been shown to be an extremely poor candidate for most of the studies in which it has been employed. The animal is a poor learner under conditions where response acquisition has been demonstrable; increasing susceptibility to amnesic agents and/or events, has been shown.

The purpose in using 3 different strains of the genus Mus musculus, is to provide for age differences as well as differences which, in the mature mouse, occur in relation to amnesia susceptibility.

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Animals from the designated strains will be utilized from 16 to 35 days of age and the specific experiments will concern: (1) effects of nicotine and its active metabolites upon memory consolidation during early development among several strains of the genus Mus musculus. Effects of two amnesic treatments will be independently assessed in this group of mice. Transcorneal ECS or intrahippocampal 5-HT, as have been previously documented in the CF-1S mouse, which in present studies will constitute a baseline, will be given following single trial passive avoidance conditioning

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in nicotine treated mice. The temporal gradient for the expected retrograde amnesia effect of such treatments will be assessed as a function of age in which stress relationship emerges between drug treatment and the antagonism of retrograde amnesia will allow for the specification of the parameters within which subsequent experiments may be carried out; (2) Identification of the temporal relationship between the effect of nicotine and/or metabolites and cerebral amine metabolism. On the basis of previous findings, it seems appropriate to pursue the hypothesis that nicotine induced antagonism of a retrograde amnesia stimulus depends upon the ability of such treatment to block the neurochemical sequela of the amnesic stimulus. Such sequela have been specifically, brain biogenic amines, notably 5-hydroxytryptamine. Therefore, in relation to the time course of the aminergic effect of nicotine on several agents in several strains of mice, the interaction will be studied for both ECS and intrahippocampal 5-HT as predictable amnesic-inducing agents. (3) Specific cellular effects of nicotine and these metabolites as related to memory consolidation in several strains of mouse during late development. The relationship between developmental age and the susceptibility of amnesic agents or events has emerged as dependent upon the status of brain amines, their lability in relation to amnesic stimuli, and the influence of such alterations upon cerebral protein synthesis at specific cellular sites. This series of experiments will be directed toward the elaboration of age and strain variables as they contribute to amine regulation of protein synthesis. This relationship will be explored in animals treated with nicotine and several of its active metabolites and the effects of such treatment upon 5-HT-and protein synthesis-changes produced by amnesic stimuli. These relationships will be examined on a regional, cellular and subcellular level and if sufficient time permits, attempts will be further made at the identification of the proteins, which for specific age populations or strains, becomes resistent and/or susceptible to inhibition by amnesic stimuli.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Two air-conditioned laboratories with adjoining vivarium facilities are currently in use by the investigator. All equipment necessary for the behavioral and biochemical procedures involved with this proposal are available and no additional equipment needs are anticipated for the duration of this project.

11. Additional facilities required:

NONE

12. Biographical sketches of investigator(s) and other professional personnel (append): See Page 3a.

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

See Page 3b.

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12. Biographical Sketch of Investigator:

WALTER B. ESSMAN

Education:

Ph.D. - University of North Dakota, R (Major: Psychology; Minor: Medical Sciences)

M.D. - (Cum Laude) - University of Milan, R

M.A. - University of North Dakota, R

B.A. - New York University, R

Experience:

Professor (Psychology, Biochemistry), Queens College of the City University of New York, 1967 - Present.

Associate Professor, Queens College of the City University of New York, 1965-66.

Assistant Professor, Queens College of the City University of New York, 1962-64.

Research Professor, Neurology, Mt. Sinai School of Medicine, New York, 1972 - Present.

Research Associate, Laboratory of Neurochemistry, Mt. Sinai School of Medicine, New York, 1966-72.

Research Fellow, Laboratory of Neurochemistry, Mt. Sinai Hospital, New York, 1964-66.

Research Assistant Professor, Dept. of Rehabilitative Medicine, Albert Einstein College of Medicine, 1962-63.

Research Associate, Dept. of Physiology, Albert Einstein College of Medicine, 1961-63.

Senior Post-Doctoral Fellow, Neurophysiology, Albert Einstein College of Medicine, 1959-61.

Director, Psychophysiological Research, U.S. Army Surgical Research Unit, 1958-59.

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13. Publications (5 most recent):

1. Essman, W.B. Neurochemistry of Cerebral Electroshock. New York: Spectrum Publ., 1973.

2. Essman, W.B. Neuromolecular modulation of experimentally induced retrograde amnesia. Confinia Neurol., 1973, 35: 1-22.

3. Essman, W.B. Effects of ECS on cerebral protein synthesis. In: Fink, M., Kety, S.S., McGaugh, J., & Williams, T. (Eds.). The Psychobiology of Convulsive Therapy. Washington, D.C.: V.H. Winston & Sons, 1974, 237-249.

4. Essman, W.B. Drug effects and learning and memory processes. In: Garattini, S. and Shore, P. (Eds.). Advances in Pharmacology and Chemotherapy. New York: Academic Press, 1971, Pp. 241-330.

5. Essman, W.B. Changes in cholinergic activity and avoidance behavior by nicotine in differentially housed mice. Int. J. Neurosci., 1971, 2: 199-206.

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14. *First year budget:*

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Dr. Walter B. Essman	100%	-----
Technical		
Traum, John - Technical Assistant	100%	REDACTED
Rosenthal, Richard -- Assistant	50%	
+16% Fringe Benefits		
Sub-Total for A		

B. Consumable supplies (by major categories)

Animal Purchases	800.
" Cleaning, Bedding	600.
Chemicals, Glassware	840.
Disposable Cages	450.
Sub-Total for B	$2,690.

C. Other expenses (itemize)

International Symposium on Memory Processing, Milan, Italy, June '74	
Endocrine Society, Chicago, Ill., June '74	
American College of Neuropsychopharmacology, San Juan, Puerto Rico, Dec. '74.	
Sub-Total for C	$1,100.
Running Total of A + B + C	$19,624.

D. Permanent equipment: (itemize)

NONE

Sub-Total for D	-----
E	$ 2,943.60
Total request	$22,567.60

E. Indirect costs (15% of A+B+C)

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	R	$2,690.	$1,100.	---	$2,943.60	$22,567.60
Year 3		$2,690.	$1,100.	---	$2,943.60	$22,567.60

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16. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Metabolic Response to Stress -- Tobacco Smoke Interactions	RF-09358 C.T.R. #836A	$44,000.	10/1/73 - 9/30/74
Role of Nicotine Action Upon Memory Consolidation	RF-09410 C.T.R. #623BR1	$21,579.	4/1/73 - 3/31/74

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Walter B. Essman, M.D., Ph D.

Signature [redacted] Date 11/15/73

Telephone [redacted] (Area Code / Number / Extension)

Checks payable to

Research Foundation of C.U.N.Y.

Mailing address for checks

Mr. Paul Segall, Comptroller
Research Foundation of C.U.N.Y.
1411 Broadway
New York, N.Y. 10018

Responsible officer of institution

Typed Name 1. Hannah Petzenbaum
2. David H. Speidel

Title 1. Research Foundation - Queens College
2. Associate Dean of the Faculty - Q.C.

Signature 1. [redacted] Date 11/16/73
2. [redacted]

(Area Code / Number / Extension)

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